The Examiner rejected claims 25-28 under 35 U.S.C. § 112, first paragraph as containing subject matter not described in the specification in a way to reasonably convey to a person skilled in the art that the inventors had possession of the invention at the time that the application was filed. Specifically, the Examiner has noted the phrases "fully crosslinked" and "exogenous polypeptide growth factor." Applicants believe that the Examiner has fallen short of extablishing prima facie lack of written description. Applicants respectfully request reconsideration of the rejection based on the following comments.

With respect to "fully crosslinked", the Examiner asserts that "no organic reactions go to 100% completion." Applicants believe that this is incorrect. Presumably, the Examiner is referring to the fact that, in principle, all reactions are governed by an equilibrium. However, in many instances, the back reactions are, for all practical purposes, negligible, such that reactions do go to completion. For example, carbon dioxide and water do not spontaneously react to form hydrocarbons and oxygen. If the Examiner maintains this rejection, Applicants request support for the Examiner's assertions and a clear explanation of why the Applicants' position is not supported by the specification as filed.

With respect to the word "exogenous", Applicants note that the definition of exogenous from Merriam Webster's Collegiate Dictionary, tenth edition, (attached) is "introduced from or produced outside the organism or system; *specif*: not synthesized within the organism or system." Applicants believe that it is implied throughout the specification that the growth factors are introduced from outside the tissue. Also, in many locations in the specification, it is explicit that the growth factors are introduced. Specifically, from page 9, line 30 to page 12, line 13 sources of VEGF are described. Commercial sources of VEGF at page 11, lines 31-33 are clearly exogenous. The Examples in Applicants' specification further describe the use of VEGF from commercial sources.

In addition, the Examiner seems to be using an incorrect standard to evaluate the written description requirement. The Examiner asserts that the specification does not "explicitly disclose" the subject matter. It is well established that a literal, i.e., explicit, description is not needed to satisfy the written description requirement. See MPEP 2163.02. To the extent that the Examiner is requiring a literal/explicit description in the specification, the Examiner is using the wrong standard.

As explained above, the specification fully supports the claim terminology indicated by the Examiner. Applicants respectfully request withdrawal of the rejection of claims 25-28 under 35 U.S.C. § 112, first paragraph as containing subject matter not described in the specification in a way to reasonably convey to a person skilled in the art that the inventors had possession of the invention at the time that the application was filed.

Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 25-28 under 35 U.S.C. § 112, second paragraph for indefiniteness. Specifically, the Examiner has indicated that the terms "fully crosslinked" and "exogenous" are unclear. These terms have been discussed above with respect to written description. With respect to "fully crosslinked," the Examiner's assertions seem to be based on factually incorrect statements. With respect to "exogenous," the dictionary definition of the term is completely clear in context. The Examiner has failed to state a case for prima facie indefiniteness. Applicants respectfully request withdrawal of the rejection of claims 25-28 under 35 U.S.C. § 112, second paragraph for indefiniteness.

Rejection Under 35 U.S.C. §102(b) or Alternatively §103(a) Over Cahalan

The Examiner rejected claims 25 and 28 as being anticipated by Cahalan US 5,308,641 (the Cahalan patent), or alternatively, as being obvious over the Cahalan patent. The Examiner

cited the Cahalan patent for disclosing human or animal tissue and growth factors. Further, the Examiner noted that light crosslinking might be "fully crosslinking" to the extent defined and described in the Cahalan specification. Applicants maintain that Applicants' invention is not disclosed by the Cahalan patent, and thus the Cahalan patent does not render Applicants' invention prima facie anticipated or obvious. Applicants respectfully request reconsideration of the rejection based upon the following comments.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently, in a single prior art reference." (MPEP 2131 citing *Verdegaal v. Union Oil Co. of California).*

The Cahalan patent discloses light crosslinking of the polyalkylimine, such that aldehyde linkages can be provided at the interface between the biomolecule and the polyalkylimine, so the biomolecule can readily bond (lightly crosslinked) to the polyalkylimine. (see Abstract, column 3, lines 14-20, column 4, line 66 to column 5, line 3). As such, the Cahalan patent discloses light crosslinking of polyalkylimine; the Cahalan patent does not disclose fully crosslinked **tissue**. Since the Cahalan patent does not disclose, teach or suggest **fully crosslinked tissue**, the Cahalan patent does not prima facie anticipate Applicants' claimed invention. With respect to light crosslinking, this type of crosslinking in the Cahalan patent cannot cover fully crosslinked tissue since the Cahalan patent describes light crosslinking as requiring "just a few minutes." See column 5, lines 9-10. Certainly, "light crosslinking" cannot inherently disclose fully crosslinked since "light crosslinking" does not necessarily result in full crosslinking.

Furthermore, the Examiner asserts that "light crosslinking" is only a preferred embodiment in the Cahalan patent and that it would be obvious to proceed to fully crosslinking the polyalkylimine. Applicants believe this is a misunderstanding of the Cahalan patent, and that light crosslinking is described as an aspect of reaching the objective of linking a biomolecule to the polyalkylamine (see, for example, abstract, column 3, lines 13-20, column 4, lines 66 to

column 5, line 3; column 7, lines 45-50 Example 5). Light crosslinking of the polyalkylimine ties-up some of the polyalkylimine sites via the aldehyde functionality of the crosslinking agent, but not all of the sites, so that some imine groups are available to bond the biomolecule to the polyalkylimine. Though the Cahalan patent teaches lightly crosslinked polyalkylimines, the Cahalan patent does not teach, suggest, or motivate **fully crosslinked tissue**. Specifically with respect to lack of motivation, the objectives in the Cahalan patent are completely unrelated to the modification of material properties that would generally result from full crosslinking. With respect to the Examiner's assertions that light crosslinking is only a preferred embodiment, Applicants note that at column 5, lines 9-10, light crosslinking is described with respect to the time to achieve the crosslinking, not as a preferred crosslinking time. Thus, the preferred aspects in other places in the Cahalan patent do not seem to be related to the light crosslinking.

Since the Cahalan patent does not teach, suggest or motivate Applicants' claimed invention, the Cahalan patent does not render Applicants' claimed invention obvious. Applicants respectfully request withdrawal of the rejection of claims 25 and 28 under 35 U.S.C. §102(b) as anticipated or, alternatively, under 35 U.S.C. §103(a) as being unpatentable over the Cahalan patent.

Rejection Under 35 U.S.C. §102(b) as Anticipated by Bayne et al.

The Examiner rejected claims 25 and 26 under 35 U.S.C. §102(b) as being anticipated by the Bayne et al. European Patent application 0476983 (the Bayne EP application). The Examiner asserts that the Bayne EP application discloses applying fibrin coating prior to the VEGF II coating onto the surface of the fixed umbilical vein, since the tubular supports include fixed umbilical vein. Applicants believe that this is a misunderstanding of the Bayne EP application. Applicants respectfully request reconsideration of the rejection based upon the following comments.

Upon close reading of the Bayne EP application, it is noted that after an adequate number of endothelial cells are grown, these cells are plated on the inside surface of the fixed umbilical vein. No mention is made of prior coating of the umbilical vein with VEGF II or a protein like fibrin. The Bayne EP application then states that "Following implantation endothelial cells...grow on the **artificial surface.** Prior coating...with proteins such as fibrin...enhance attachment to the **artificial surface.**" (emphasis added) (page 8, lines 17-23). The Bayne EP application does not disclose application of a growth factor (rather than cultured cells) to a fixed tissue. Since the Bayne EP application does not disclose at least one element of the claimed invention, the Bayne EP application does not prima facie anticipate Applicants' claimed invention.

Since the Bayne EP application does not disclose fixed tissue associated with a polypeptide growth factor, the Bayne EP application does not anticipate Applicants' claimed invention. Applicants respectfully request the withdrawal of the rejection of claims 25 and 26 under 35 U.S.C. §102(b) as being anticipated by the Bayne EP application.

Rejection under §103(a) Over the Bayne EP Application

The Examiner alternatively rejected claims 25 and 26 as unpatentable under 35 U.S.C. §103(a) over the Bayne EP application. The Examiner asserts that if the tubular supports coated with VEGF II do not include umbilical vein, then it would have been obvious to use umbilical vein as the tubular support. Applicants believe that upon close reading, the Bayne EP application does not teach, suggest or motivate the association of fixed (fully crosslinked) tissue with a polypeptide growth factor, in particular with VEGF. Applicants respectfully request reconsideration of the rejected claims based upon the following comments.

The Bayne EP application teaches the association of VEGF II with an **artificial surface** (page 8, lines 20-23). When referring to a fixed umbilical vein, no mention is made of the use of

VEGF II. The very short discussion in the Bayne EP application does not teach, suggest or motivate application of VEGF with a fixed tissue, which is not an artificial surface.

Since the Bayne EP application does not teach, suggest or motivate the association of a polypeptide growth factor such as VEGF II with a fixed (fully crosslinked) tissue, the Bayne EP application does not render Applicants' claimed invention obvious. Thus, the Examiner has not asserts a prima facie case of obviousness. Applicants respectfully request withdrawal of the rejection of claims 25 and 26 under 35 U.S.C. §103(a) as being unpatentable over the Bayne EP application.

Rejection Under 35 U.S.C. §103(a) as being Unpatentable over Bayne et al. in View of Wadström

The Examiner rejected claims 1-2, 4-5, 9-11, and 29 under 35 U.S.C. §103(a) as being unpatentable over Bayne et al. EP0476893 (the Bayne EP application) in view of Wadström US 5,631,011 (the Wadström patent). The Examiner asserts that the Bayne EP application discloses a fixed tissue coated with a fibrin coating (biologic adhesive) that is applied prior to the application of a polypeptide growth factor, VEGF, and the Wadström discloses fibrin as a common biologic tissue adhesive. The Examiner asserts that it would have been obvious to use an allograft or xenograft tissue for the umbilical vein disclosed in the Bayne EP application. Applicants respectfully request reconsideration of the rejection of claims 1-2, 4-5, 9-11 and 29 based upon the following comments.

The Bayne EP application does not disclose a polypeptide growth factor or protein such as fibrin associated with the umbilical vein, as discussed above. Similarly, the Wadström patent does not teach, suggest or motivate association of a polypeptide growth factor with tissue. Since the Bayne EP application and the Wadström patent do not teach, suggest or motivate the association of polypeptide growth factor with tissue, it would not be obvious to associate a

polypeptide growth factor with allograft or xenograft tissue. Thus, the combined disclosures of the Bayne EP application and the Wadström patent do not render the claimed invention obvious.

In addition, the Wadstrom patent does not disclose the use of a biologic adhesive to associate a growth factor with a material. The Bayne EP application does not teach, suggest or motivate the use of an adhesive to associate a growth factor with a substrate. The Examiner asserts that fibrin is a polymer. That is correct, but fibrin is not an adhesive. A mixture of fibrinogen and thrombin is an adhesive, which can be called a fibrin adhesive since fibrin is formed in the reaction. Once fibrin is formed, the adhesive properties are no longer present since the fibrin protein itself is not adhesive. The combined disclosures of the Bayne EP application and the Wadstrom patent do not teach, suggest or motivate association of a polypeptide growth factor with a substrate using an adhesive.

Since the references do not teach, suggest or motivate the claimed invention, Applicants respectfully request the withdrawal of the rejection of claims 1-2, 4-5, 9-11, and 29.

Rejection Under 35 U.S.C. §103(a) Over Bayne et al., Wadström and Carpentier et al.

The Examiner rejected claims 6-8, 14, 15, 21-24, and 27-28 under 35 U.S.C. §103(a) as being unpatentable over the Bayne EP application and the Wadström patent as applied to claims 1-5, 9-11, and 29, and further in view of U.S. Patent 4,648,881 to Carpentier et al.(the Carpentier patent). The Examiner cited the Carpentier patent for disclosing uncrosslinked and crosslinked tissue, heart valve tissue and other types of tissue. The Examiner asserted that it would have been obvious to use these materials as the substrates within the teaching of the Bayne EP application for the application contemplated by Carpentier. Applicants respectfully request reconsideration of the rejections based upon the following comments.

The Bayne EP application does not disclose the tissue, such as fixed umbilical vein, with the growth factor or an adhesive or specific binding interactions to associate a protein with a

substrate. The Wadström patent does not teach or suggest the use of a biologic adhesive for association of active biomolecules with a substrate. The Carpentier patent discloses treatments of tissue to reduce the incidence of calcification and does not disclose the association of biologically active proteins with tissue. Thus, the references do not teach, suggest or motivate association of growth factors with valved protheses or the association of biologically active molecules with a substrate using a biological adhesive. In addition, the combined disclosures do not provide a reasonable expectation of success with respect to Applicants' claimed invention. Since the combined disclosures do not teach, suggest, or motivate elements of Applicants' claimed invention and do not provide a reasonable expectation of success with respect to Applicants' claimed invention, the combined disclosures of the cited references do not render claims 6-8, 14, 15, 21-24, and 27-28 obvious.

In view of the above comments, Applicants respectfully request withdrawal of the rejection of claims 6-8, 14, 15, 21-24, 27 and 28 under 35 U.S.C. §103(a) as being unpatentable over the Bayne EP application and the Wadström patent as applied to claims 1-5, 9-11 and 29, and further in view of the Carpentier patent.

CONCLUSIONS

In view of the foregoing, it is submitted that this application is in condition for allowance. Favorable consideration and prompt allowance of the application are respectfully requested.

The Examiner is invited to telephone the undersigned if the Examiner believes it would be useful to advance prosecution.

Respectfully submitted,

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August 19, 2002
Date

Shari Thorndike